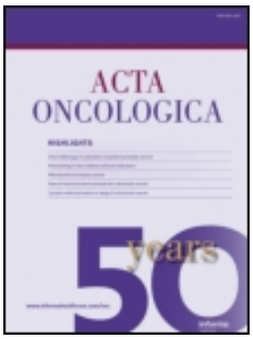

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Prospective evaluation of the palliative effect of whole-brain radiotherapy in patients with brain metastases and poor performance status

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ORIGINAL ARTICLE

Prospective evaluation of the palliative effect of whole-brain radiotherapy in patients with brain metastases and poor performance status

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Abstract

Background/Purpose. The benefit of whole brain radiotherapy (WBRT) for RTOG RPA (Radiation Therapy Oncology Group Recursive Partitioning Analysis) class 3 patients with brain metastases is not well established. The aim of this study was to determine whether WBRT has any benefit in terms of symptoms palliation in such patients. Evaluation of patients' preferences for WBRT, changes in performance and neurological status were secondary aims. *Methods.* Ninety-one RTOG RPA class 3 patients were included. All patients received WBRT (20 Gy in 5 fractions) and were asked to complete a questionnaire about their symptoms before and one month after WBRT. The patient's symptom checklist comprised 17 items scored from 0 to 3; a higher score meant a greater symptom intensity. The mean scores at baseline and after treatment were compared. Karnofsky performance status (KPS) and neurological status before and one month after WBRT were also recorded. Patients were asked to express their preference as to the WBRT undergone. *Results.* Forty-three (47%) patients completed both symptom checklists. The mean scores on the symptom checklist were 18.21 and 21.09 at baseline and one month after WBRT, respectively ($p = 0.02$). The KPS was estimated after WBRT in 42 patients: 57% of patients improved, 26% worsened, and 17% did not change from the baseline KPS score ($p = 0.06$). Neurological status did not change from baseline to one month after WBRT ($p = 0.44$). Only 7% of respondents would not have consented to the WBRT undergone. *Conclusion.* Our results challenge the palliative value of the WBRT in RPA class 3 patients.

Non-randomized studies suggest that whole-brain radiotherapy (WBRT) in patients with brain metastases increases median survival compared with supportive care only [1,2]. Symptom palliation after WBRT has been reported in 60–80% of patients in retrospective studies [3,4]. However, only 19% of patients report improvement in symptoms when symptoms are evaluated prospectively [5].

Recursive partitioning analysis (RPA) identified three prognostic classes from the Radiation Therapy Oncology Group (RTOG) brain metastases prospective trials. This classification is based on the presence of three prognostic factors: performance status, status of extracranial disease (primary and extracranial metastases), and age [6]. The prognosis is poorest for RPA Class 3, which includes all patients with a score on the Karnofsky performance scale (KPS) [7] of less than 70; that is, individuals considerably or completely dependent on others. The median survival for such patients is estimated to be approximately two months [6,8]. The use of supportive care alone without WBRT may be an option for these patients, given their short life expectancy.

The magnitude of the benefit of WBRT over steroids alone remains unknown for this subset of patients. The old trial of Horton et al. [9] comparing steroid use only with the WBRT in a small group of patients in the pre-CT era showed no difference between the two modalities. For practical reasons, it is impossible to conduct a randomized trial to evaluate the benefit

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of WBRT over supportive care only in these patients. However, because a symptom relief is a main goal of all management in this population, the symptom palliation may reflect the value of WBRT in RPA class 3 patients.

The aim of this study was to evaluate prospectively the symptom burden, as rated by RPA class 3 patients undergoing WBRT. The secondary aims of the study were to evaluate the patients' preferences for the WBRT undergone and the observer-rated changes in performance and neurological status after WBRT in this subset of patients.

Patients/Methods

Patients and study design

The study was approved by the institutional ethics committee.

The inclusion criteria were as follows: radiologically diagnosed brain metastases using brain CT or MRI, KPS score < 70 (RPA class 3), and signed informed consent to participate in the study. The exclusion criteria included significant speech or cognitive impairment preventing the patient from completing the questionnaire, KPS < 30 (in our opinion, such a score rendered patients not suitable for WBRT), prior surgery for brain metastases, previous WBRT and/or radiosurgery, or brain metastases from a hematological malignancy.

Patients who met the inclusion criteria and qualified for WBRT were asked to complete a symptom checklist. This checklist of 17 items was translated into Polish from the work of Bezjak et al. [5]. As in the original work, the goal was to capture the symptoms related to brain metastases and intracranial hypertension (eight items: headache, nausea, vomiting, leg weakness, arm/hand weakness, balance problems, difficulty of walking, and speech disorders); possible side effects of steroid use (four items: dyspepsia, insomnia, mood disorders, and weight gain); and possible side effects of WBRT (four items: fatigue, anorexia, hair loss, and hearing impairment). The final question was open ended and asked the patients to describe in free text any other health problem that significantly impaired their life activity from their point of view. Patients scored the intensity of each symptom on a four-point categorical scale (from 0 = not at all to 3 = very much), thus a higher score indicated more severe symptoms (Appendix 1). The baseline symptom checklist was completed before the start of WBRT but after at least 48 hours of steroids use. The help of the patients' relatives, but not of the medical staff, in the completing the questionnaire was allowed. The baseline evaluation of performance (KPS) and neurological status was performed by the attending radiation oncologist before the start of WBRT. Neurological status was assessed using the Medical Research Council (MRC) scale (Appendix 2) [10]. The main reason for impairment of performance status was recorded by selecting the appropriate item: "brain metastases", "extracranial disease", or "brain metastases and extracranial disease".

WBRT was given using opposing lateral fields on a cobalt unit or a linear accelerator. The total dose of WBRT was 20 Gy in 5 fractions and five days. The recommended dose of steroids at the start of WBRT was 12 mg of dexamethasone per day. If a higher dose of steroids was needed or the lower dose significantly improved neurological condition, the doses were not modified but were recorded. The progressive tapering of steroid dose after WBRT and use of gastric protection was recommended.

The response to WBRT was assessed one month after WBRT completion. Patients were asked to complete the same symptom checklist as at the baseline and return it at the follow-up visit to the radiation oncologist or to mail it to the treating center in the stamped and addressed envelope given at the entry to the study, if they were not able or willing to attend the follow-up visit. There were two additional questions attached to the symptoms checklist; the first one was about the general evaluation of symptom palliation by the WBRT, and the second one was about the patient's willingness to undergo the WBRT as the treatment of choice of brain metastases given his or her experience with this treatment (Appendix 1). If a patient did not attend the follow-up visit and the questionnaire was not received by a treating physician within one week after the one month (i.e., one month and one week after WBRT), the patient or the family was contacted by telephone, and information about symptom evolution, performance, neurological status and steroids dose was collected. Each time, if the patient was able, we requested the patient to complete the questionnaire and mail it. At the one-month follow-up visit, performance, neurological status, and current steroid dose were recorded as at the baseline.

Statistical analysis

The primary endpoint of the study was the change in symptom score from baseline to one month after completion of WBRT. We arbitrarily defined a clinically meaningful change after WBRT as a 25% change in score from the baseline. The sample calculation was calculated initially at 90 patients. Based on the work of Bezjak et al. [5], we expected a response rate of about 50%, and with an α-value of 0.05 and a β-value of 0.8, we needed about 40 pairs of questionnaires from patients to detect this difference.

This gave a required n of 80, and an additional 10 were included to allow for expected dropouts because of the poor prognosis in these patients. Differences in the mean score on the symptom checklist from before to after WBRT were analyzed using the paired *t*-test for dependent samples. The Wilcoxon signed-rank test was used to analyze the changes in KPS and MRC neurological scores. Additional analyses were performed on the differences in scores of symptoms separately for subgroups depending on the reason for the impairment shown in the KPS (e.g., related to brain metastases vs. extracranial disease and both).

The changes in symptom scores were analyzed separately for the three domains: symptoms related to brain metastases and/or intracranial hypertension, steroid side effects, and WBRT side effects. These were analyzed by paired *t*-test to identify which symptom cluster was the most burdensome for patients and influenced the general score. Finally, we tested for differences in scores for all items separately to identify which symptom improved the most following WBRT. As for most symptoms analyzed separately, the data were not distributed normally, we analyzed these data using the Wilcoxon signed-rank test. The patients' preferences for treatment and responses to direct questions about symptom palliation were compared with a change in the scores of the symptom checklist and observer-rated changes in performance and neurological status.

All calculations were carried out using StatSoft/ Statistica 6.0.statistical software package.

Results

From 2005 to 2007, 91 patients were included in the study. The patients' characteristics are given in Table I. All patients were on corticosteroids at the start of WBRT. Two centers began the study, but one of the centers stopped accrual after including nine (10%) patients. The median survival was 2.0 months (range: 0.05–10.0 months). All patients died at the time of the analysis. Three deaths occurred during WBRT.

Patient-rated symptom evaluation

Forty-three (47%) patients completed both symptom checklists and were included in the quantitative evaluation of the efficacy of WBRT in RPA class 3 patients. The reasons for not completing the second questionnaire in the other 48 (53%) patients were as follows: death within one month after WBRT in 25 (52%) patients, deterioration of cognitive function preventing completing of the questionnaire in seven (15%), deterioration of performance status preventing completion of the questionnaire in three (6%), and unknown reasons in 13 (27%).

Table I. Patients' (n = 91) characteristics at baseline.

Characteristic	Number (%) unless otherwise stated
Sex	
Male	51 (56)
Female	40 (44)
Age	
Median (range), years	66 (39–86)
Primary	
Lung	59 (65)
Breast	14 (15.5)
Unknown primary	12 (13.5)
Colon	4 (4)
Cervix	2 (2)
KPS* score	
60	59 (65)
50	20 (22)
40	12 (13)
Neurological MRC# score	
1	1 (1)
2	6 (7)
3	62 (68)
4	22 (24)
Presence of extracranial disease	
Yes	36
No	27
Not investigated	28
Main cause of the deterioration of the KPS* score	
Brain metastases	63
Extracranial disease	3
Both	25

*KPS – Karnofsky Performance Status
#MRC – Medical Research Council

The mean score of the baseline symptom checklist for the 43 patients was 18.21 (standard deviation [SD]: 6.23), and the mean score for these patients one month after WBRT was 21.09 (SD: 7.00) ($p = 0.02$), indicating worse functional outcome after WBRT. Fifteen (35%) patients had a lower symptom score after treatment, with average improvement of 28% (range: 4–75%), and 27 (60%) patients had a higher symptom score, with average worsening of 60% (range: 9–188%) from baseline. The mean score on the baseline symptom checklist did not differ between the 43 patients who completed both questionnaires and the 48 patients who completed only the first questionnaire (mean: 17.34, SD = 5.99) ($p = 0.79$).

For particular subgroups of symptoms on the checklist, the mean scores did not differ between baseline and after treatment, except for subgroup of four items attributable to WBRT side effects which increased significantly after treatment from a baseline mean of 3.25 (SD: 2.12) to 5.79 (SD: 2.35) at follow-up ($p < 0.00001$). The mean scores for the eight items related to brain metastases or intracranial hypertension were 10.89 (SD: 4.00) at baseline and 10.30 (SD: 3.86) at follow-up ($p = 0.48$). The scores for the four items of symptoms related to steroid use were 3.56 (SD: 2.52) at baseline and 4.11 (SD: 2.61) at follow-up ($p = 0.22$).

Table II. The changes in scores from before to after WBRT for particular items listed in the symptoms checklist.

Symptoms	Mean score before WBRT (SD)	Mean score one month after WBRT (SD)	P-value
Symptoms related with a high probability to the presence of metastases or intracranial hypertension			
Headaches	0.80 (0.95)	0.86 (0.89)	0.81
Nausea	0.33 (0.69)	0.21 (0.52)	0.26
Vomiting	0.28 (0.63)	0.05 (0.21)	**0.02**
Leg weakness	2.21 (1.08)	2.42 (0.82)	0.31
Arm/hand weakness	1.86 (0.99)	1.77 (1.04)	0.62
Balance problems	2.07 (1.16)	2.05 (1.01)	0.92
Difficulty walking	2.38 (0.91)	2.38 (0.88)	0.99
Speech disorders	0.93 (1.20)	0.62 (1.01)	0.09
Symptoms related with a high probability to steroid use			
Dyspepsia	0.40 (0.66)	0.37 (0.72)	0.84
Insomnia	1.26 (1.09)	1.23 (1.07)	0.90
Mood disorders	1.44 (1.03)	1.65 (1.11)	0.33
Weight gain	0.48 (0.89)	0.98 (1.09)	**0.03**
Symptoms related with a high probability to the side effects of WBRT			
Hair loss	0.26 (0.66)	2.21 (0.98)	**<0.00001**
Hearing loss	0.54 (0.94)	0.67 (0.90)	0.54
Anorexia	0.83 (1.00)	0.86 (1.10)	0.91
Fatigue	1.63 (1.04)	2.12 (1.05)	**0.02**
Others			
Other symptoms	0.87 (1.29)	0.70 (1.11)	0.45

The changes in scores for particular items from before to after WBRT are summarized in Table II. Among the eight symptoms attributable to the presence of brain metastases, only vomiting improved significantly (mean: 0.28 before treatment vs. 0.05 after treatment, $p = 0.02$). The symptoms attributable to steroid use did not change significantly, except for weight gain, which worsened after WBRT (mean: 0.48 before treatment vs. 0.98 after treatment, $p = 0.03$). For symptoms attributable to the side effects of WBRT, hair loss (mean: 0.26 before treatment vs. 2.21 after treatment, $p < 0.00001$) and fatigue (mean: 1.63 before treatment vs. 2.12 after treatment, $p = 0.02$) worsened after treatment.

Thirty-two patients of 43 patients who completed both checklists showed an initial deterioration of performance status caused by the presence of brain metastases only. We found no benefit of WBRT in this subgroup of patients because the change (worsening) of their scores (mean: 18.31 before vs. 21.53 after, $p = 0.03$) did not differ from the change in the entire group.

Observer-rated performance, neurological status, and steroid taper

The performance status was assessed by attending physician one month after treatment in 42 patients: 32 patients who completed both checklists and 10 who did not complete the second checklist. These discordances were related to the fact, that some questionnaires were mailed and patients were not assessed by physicians and some patients attended follow-up visit but were not able to complete a questionnaire. The KPS scores improved in 24 (57%) patients, worsened in 11 (26%), and did not change in seven (17%) ($p = 0.06$). Neurological status one month after treatment was assessed in 44 patients: 35 patients who completed both checklists and nine who did not complete the second questionnaire. The MRC score improved in 15 (34%) patients, worsened in 12 (27%), and did not change in 17 (38%) ($p = 0.44$). The observer-rated changes of KPS score did not correspond to the patient-rated changes of symptom scores. This was because, in the 20 patients who's KPS score improved, 10 had improved symptom scores and 10 had worse symptom scores, and in the seven patients whose KPS scores worsened, three had improved symptom scores and four had worse symptom scores.

Steroid taper was recorded in 41 patients; the dose decreased in 28 (68%) patients, remained the same in six patients, and increased in seven patients.

Patients' preferences for treatment and responses to the question about symptom palliation

Thirty-nine respondents answered the direct question about improvement of symptoms after WBRT. Twenty-nine (75%) patients reported improvement of symptoms (41% major improvement and 34% slight improvement), six (15%) reported no change, and four (10%) reported worse symptoms. These responses did not correspond with the changes in scores on the symptom checklist because 13 of the 29 patients who

reported improvements had higher scores and 12 had lower scores. In 10 patients who reported no change or worse symptoms, six had higher scores and three lower scores in symptom checklists. Similarly, the patients' perceptions about the evolution of their symptoms in the direct questions did not correspond with the physicians' evaluations of performance status. Of the 10 patients whose KPS was rated as worsened or not improved, six reported improvements, three reported no change, and only one reported worse symptoms.

Forty patients answered the question about their hypothetical consent to undergo the WBRT given their experience: 16 (40%) would have consented to the WBRT, 21 (53%) would have left this decision to the treating physician, and only 3 (7%) would not have consented to the WBRT.

Discussion

The symptom burden increased significantly in RPA class 3 patients one month after WBRT. The general score of patient-rated symptoms might have been compromised by the evaluation of one item—hair loss—which is an evident concern after WBRT. However, no one symptom, especially in the brain metastases-related subgroup, improved after treatment except for vomiting. For vomiting, this was a very small number of events (shown in the low mean score), which might, in the context of multiple comparisons, increase the statistical hazard bias. Even if we exclude hair loss, which is questionable because this is a concern for all patients, we still found no palliative effect of WBRT in our respondents.

The high rate of no response is similar to that observed in most palliative studies and is a limitation of questionnaire-based trials. However, in the case of 38% of documented deaths and profound deteriorations of health preventing from completion of the second questionnaire, we should admit that the general result was much worse, if even more fortunate alive patients had still more complaints after than before treatment. Bezjak et al. also found no benefit of WBRT for most patients with brain metastases [5] using the same evaluation tool. Chow et al. [11] reported that some aspects of QoL, such as fatigue, drowsiness, and appetite, worsened significantly after WBRT in patients with brain metastases. The severity of these symptoms and nausea increased over time up to 12 weeks after WBRT [12]. The transient demyelination of white matter following WBRT causes somnolence syndrome and loss of appetite [13]. Symptoms caused by subacute radiation injury last longer (up to six months) than the expected survival of RPA class 3 patients. Hearing loss and alopecia may also impact on the remaining lifetime. We acknowledge that some symptoms attributable to the WBRT, such as fatigue and poor appetite, are also related to the extracranial disease progression. In our study, fatigue was rated by patients with brain metastases as the most severe symptom before WBRT (i.e., the highest mean score of no brain metastases-related symptoms), and all respondents died from disease progression soon after the second questionnaire was completed. This suggests that at least the fatigue, which is attributable to the side effects of WBRT [5,11,12], represents a common symptom of all terminally ill patients and is probably not caused by radiation. However, such patients are unlikely to derive any benefit from WBRT.

The power of our findings may also be limited by the evaluation tool used. We did not evaluate QoL with available and validated questionnaires because of the problems evaluating QoL of terminally ill patients. The primacy given to health in most QoL questionnaires is questionable in this population. As shown by Waldron et al. [14], such patients give priority to other values such as family, company, or religion over health-related issues. Because the goal of WBRT is palliation of symptoms, we decided to evaluate the symptom burden prospectively by adopting the symptom checklist of Bezjak et al. [5], which was modified from questionnaires intended specifically for brain cancer patients. We were unable to confirm any improvement in the minority of one month-survivors and individuals judged fit enough to complete the interactive study.

Another limitation of our study is that, despite our original intention, we were unable to report the exact details of the taper of the steroid dose in all our patients.

We have been using a short fractionation schedule of 20 Gy in 5 fractions. Such a schedule is routinely used in our country for palliative brain irradiation. One may argue that with more protracted radiotherapy as used in countries with more resources, the results would be different. However, we have no data that any radiation schedule of WBRT (ranging from 20 Gy in 5 fractions to 50 Gy in 10 fractions) gives superior outcome [15–17].

Despite a worsening of general patient-rated symptoms scores, most (75%) patients reported improved symptoms in the direct question on the palliative effect of WBRT. However, a patient may not be a good judge of the effect of the particular treatment because he or she may not differentiate the effects associated with supportive care (e.g., use of steroids) from the evaluated method. The lack of correlation between the patients' general evaluation of the effect of WBRT and symptom scores and physicians' evaluation of the performance status may indicate that there were other, probably complex, reasons underlying the responses, such as the coping strategies used by patients with no curative treatment option available

and the search for hope from any treatment delivered. Despite an apparent weak response rate to the treatment, all but three patients would have consented to the WBRT, given their actual experience with treatment and its consequences, or would have left the decision to the treating physician. This may be explained by the common belief that cancer patients are often willing to accept any treatment that may give them hope. In another study using interviews, patients who had no cancer were unwilling (more often in Europe than in the US) to accept an aggressive treatment with little chance of benefit [18]. When the cancer patients were asked the same question, they were more willing to accept an aggressive treatment with a weak chance of positive effect, and there was no difference between patients in Europe and the US.

Considering the heavy burden of WBRT side effects on the general symptom intensity, the limitation of the volume of irradiated brain may be discussed in some patients. Chernov at al. [19] showed that stereotactic treatment might be beneficial for some symptomatic patients with poor performance. A subgroup of RPA class 3 patients who are likely to benefit from aggressive forms of treatment was identified: patients whose deterioration of performance status was caused by brain metastases as opposed to patients whose extracranial disease symptoms led to the deterioration of health. Similarly, we sought to determine whether patients with deterioration of performance status related to brain metastases only would benefit more from WBRT than those whose extracranial cancer progression impacted on the KPS. For the former, the possible side effects of WBRT might have been outweighed by a meaningful improvement in neurological status. However, we found that, even in patients with deterioration of performance status related to brain metastases only, the general symptoms score worsened because the symptoms related to brain metastases did not change but the severity of symptoms attributed to the WBRT increased. We make this statement cautiously because of the small number of events analyzed and the statistical hazard of multiple comparisons between subgroups. On the other hand, short survival (less than six months) of patients with poor performance status after aggressive treatment such as radiosurgery is also considered as a reason for not performing such aggressive and expensive forms of treatment [20].

We are aware that non-randomized character of our study weakens the strength of our conclusions. However, on the basis of our findings, we conclude that our study does not support the routine use of WBRT in RPA class 3 patients. We should give patients reliable information about the treatment side effects and the risk of a lack of a positive effect of the treatment. On the other hand, the patients' preferences for a treatment given should also be taken into account.

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References

[1] Posner J. Management of central nervous system metastases. Semin Oncol 1977;4:81–91.
[2] Zimm S, Wampler GL, Stablein D, Hazna T, Young HF. Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. Cancer 1981;48:384–94.
[3] Sen M, Demiral AS, Cetingoz R, Alanyali H, Akman F, Senturk D, et al. Prognostic factors in lung cancer with brain metastasis. Radiother Oncol 1998; 46:33–8.
[4] Kepka L, Cieslak E, Bujko K, Fijuth J, Wierzchowski M. Results of the whole-brain radiotherapy for patients with brain metastases from lung cancer: The RTOG RPA intra-classes analysis. Acta Oncol 2005;44:389–98.
[5] Bezjak A, Adam J, Barton R, Panzarella T, Laperriere N, Wong CS, et al. Symptom response after palliative radiotherapy for patients with brain metastases. Eur J Cancer 2002;38:487–96.
[6] Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745–51.
[7] Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Evaluation of chemotherapeutic agents. MacLeod CM, editor. New York: Columbia University Press; 1949. p. 191–205.
[8] Lutterbach J, Bartelt S, Stancu E, Guttenberger R. Patients with brain metastases: Hope for recursive partitioning analysis (RPA) class 3. Radiother Oncol 2002;63:339–45.
[9] Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. Am J Roent Rad Ther Nucl Med 1971;3:334–6.
[10] Van de Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomized trial. Lancet 2005;366:985–90.
[11] Chow E, Davis L, Holden L, Tsao M, Danjoux C. Prospective evaluation of patient-rated symptoms following whole brain radiotherapy for brain metastases. J Pain Symptom Manage 2005;30:18–23.
[12] Chow E, Fan G, Hadi S, Wong J, Kirou-Mauro A, Filipczak L. Symptom clusters in cancer patients with brain metastases. Clin Oncol (R Coll Radiol) 2008;20:76–82.
[13] Steel GG. Basic clinical radiobiology. Hodder Arnold: London; 1999.
[14] Waldron D, O'Boyle CA, Kearney M, Moriarty M, Carney D. Quality of life measurement in advanced cancer: Assessing the individual. J Clin Oncol 1999;17:3603–11.
[15] Gelber RD, Larson M, Borgelt BB, Kramer S. Equivalence of radiation schedules for the palliative treatment of brain metastases in patients with favorable prognosis. Cancer 1981;48:1749–53.

[16] Chatani M, Matavoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. Strahlenther Onkol 1994;170:155–61.
[17] Tsao MN, Lloyd N, Wong R, Chow E, Rakovitch E, Laperriere N. Whole brain radiotherapy for the treatment of multiple brain metastases. Cochrane Database Syst Rev 2006;3.
[18] Extermann M, Albrand G, Chen H, Zanetta S, Schonwetter R, Zulian GB, et al. Are older French patients as willing as older American patients to undertake chemotherapy? J Clin Oncol 2003;21:3214–9.
[19] Chernov MF, Nakaya K, Izawa M, Hayashi M, Usuba Y, Kato K, et al. Outcome after radiosurgery for brain metastases in patients with low Karnofsky performance scale (KPS) score. Int J Radiat Oncol Biol Phys 2007;67:1492–8.
[20] Weltman E, Salvajoli JV, Brandt RA, de Morais Hanriot R, Prisco FE, Cruz JC, et al. Radiosurgery for brain metastases: Who may not benefit? Int J Radiat Oncol Biol Phys 2001; 51:1320–7.

Appendix 1. Patient completed symptom checklist used in our study from Bezjak et al. study [5].

Please circle the number that best describes how much each of the following bothered you in the past 24 hours

	Not at all	A little	Moderately	Very much
1. Headaches	0	1	2	3
2. Nausea (feeling sick to your stomach)	0	1	2	3
3. Vomiting (being sick to your stomach)	0	1	2	3
4. Burning in the stomach	0	1	2	3
5. Poor sleeping at night	0	1	2	3
6. Restlessness/irritability	0	1	2	3
7. Weight gain	0	1	2	3
8. Tiredness (fatigue)	0	1	2	3
9. Poor appetite	0	1	2	3
10. Hair loss	0	1	2	3
11. Decreased hearing	0	1	2	3
12. Leg weakness	0	1	2	3
13. Problems with balance	0	1	2	3
14. Difficulty walking	0	1	2	3
15. Arm or hand weakness	0	1	2	3
16. Speech problems	0	1	2	3
17. Other (please state)	0	1	2	3

Two additional questions attached to the symptom checklist were included at the one-month follow-up (only one item for each question had to be chosen).

Question on general evaluation of the effect of WBRT	Radiation therapy to the brain: 1. improved my symptoms markedly, 2. improved my symptoms slightly, 3. did not reduce my symptoms, or 4. worsened my symptoms.
Question on the patient's preferences for treatment	If you had had a second chance to choose a treatment for your symptoms, would you have consented to undergo the radiation to the brain, given your experience with this treatment? 1. I would have consented to the radiation therapy to the brain. 2. I would not have consented to the radiation therapy to the brain. 3. I would have left the decision to the doctor(s).

Appendix 2. Medical Research Council (MRC) neurological function evaluation scale [10].

1. No neurological deficit.
2. Some deficit but adequate function for useful work.
3. Deficits causing moderate functional impairment—e.g., moderate dysphasia, moderate paresis.
4. Deficit causing major functional impairment—e.g., inability to use limb, gross speech impairment, or visual disturbances.
5. Inability to make conscious response.